CORTICOSTEROIDS FOR ACUTE, SEVERE ASTHMA

H. William Kelly and Shirley Murphy

ABSTRACT: Corticosteroids have been used in the therapy of acute, severe asthma since the early 1950s. Numerous randomized, double-blind, placebo-controlled trials in adults and children have proven corticosteroids to be efficacious. Only the results from less rigorously designed trials have failed to show a beneficial effect. The onset of response, dose, and mode of administration have been relatively well defined; however, other aspects (i.e., duration of therapy, need to taper the dose, and risks of multiple short bursts) require further study. Early institution of corticosteroids in well-defined patient populations will decrease the need for hospitalizations. However, administration of corticosteroids to every patient presenting to the clinician's office or emergency room prior to aggressive bronchodilator therapy is unwarranted. All patients demonstrating an incomplete response or the inability to maintain a complete response following one to two hours of aggressive bronchodilator therapy should receive a course of corticosteroids. Courses as short as three to five days have proven efficacy in outpatients, whereas hospitalized patients usually are treated for seven to ten days. The duration of therapy depends on the individual rate of response.

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CORTICOSTEROIDS HAVE BEEN USED for asthma since the early 1950s. Although most would agree that corticosteroids are useful and should be given to patients in status asthmaticus, their use is still somewhat controversial.[1,2] It is our opinion that the literature overwhelmingly supports the use of corticosteroids for the treatment of acute, severe asthma and that careful review of the literature easily explains many of the discrepancies. Despite this, a number of questions concerning the optimal use of corticosteroids in acute, severe asthma remain, such as: (1) What is the optimal dose, dosing interval, and duration of therapy? (2) When should corticosteroids be started? (3) Which corticosteroid preparation should be used? (4) What are the risks of corticosteroid therapy?

The basic molecular genetics, cellular mechanisms, and biologic effects of the corticosteroids relevant to asthma therapy have recently been reviewed.[3] The pharmacologic effects that may be of benefit in acute, severe asthma include antiinflammatory activity, inhibition of mucus secretion, potentiation of beta-adrenergics, decreased microvascular permeability, and reduction of alveolar-arterial oxygen tension gradient and venous admixture effects.[4] Of these, corticosteroids' myriad effects on the inflammatory process are the most important and may explain some of the inconsistencies found in the literature.

There are 35 trials of corticosteroids in the treatment of acute, severe asthma in the English-language literature. We analyzed these studies to provide insight into the many issues surrounding corticosteroid use in acute, severe asthma. It is difficult to make direct comparisons between studies because no two are alike. They differ in patient population, design, and hypothesis testing. Lack of methodologic details, such as when pulmonary functions were measured in relation to beta-agonist administration, were often present. Many authors failed to provide individual patient response data. Despite these difficulties, a number of conclusions and recommendations can be made. Although all studies were reviewed, those not providing significant information are not mentioned in this article. A complete listing of all the papers can be obtained from the authors.

Efficacy

INPATIENT STUDIES

A subcommittee of the Medical Research Council of England published their report of the first randomized, double-blind, placebo-controlled trial of oral cortisone acetate for status asthmaticus in 1956. The study involved 32 patients older than 14 years of age admitted to the hospital who did not respond to 24 hours of standard therapy, including parenteral aminophylline and epinephrine as well as inhaled isoproterenol. Patients were given oral cortisone acetate 350 and 200 mg on days 1 and 2, respectively. They

H. WILLIAM KELLY, Pharm.D., is a Professor of Pharmacy and Associate Professor of Pediatrics, and a Clinical Pharmacist, Pediatric Intensive Care Unit, Children's Hospital of New Mexico, and College of Pharmacy, University of New Mexico, Albuquerque, NM 87131; and SHIRLEY MURPHY, M.D., is a Professor of Pediatrics and Clinical Professor of Pharmacy, and the Director, Pulmonary/Critical Care Division, Department of Pediatrics, School of Medicine, University of New Mexico, Albuquerque, NM. Reprints: H. William Kelly, Pharm D.

GARY MILAVETZ, Pharm.D., is an Assistant Professor, College of Pharmacy, University of Iowa, Iowa City, IA 52242

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then received a dose tapered by 25 mg/d (15 patients) or placebo (17 patients) for a total of nine days. Standard therapy was continued as necessary. Although peak expiratory flow rates (PEFRs) were obtained, they were not published. Clinical symptomatology improved more rapidly in patients receiving cortisone. A greater number of patients in the placebo group (five) than in the cortisone group (one) required the code to be broken and the treatment changed to corticosteroids if they were receiving placebo.[5]

A number of studies in adult asthmatics followed, but it was not until 1983 that Fanta et al. confirmed the original work of the Medical Research Council with another double-blind, placebo-controlled trial. In both study design and reporting of detail, their study is exemplary. Twenty patients (18–45 years old) who failed four hours of intensive, standardized emergency room therapy were randomized to receive intravenous hydrocortisone (a 2 mg/kg loading dose followed by a 0.5 mg/kg/h continuous infusion for 24 hours) or placebo. Corticosteroid therapy was started after another four hours of intensive bronchodilator therapy following admission to the hospital. All patients received oxygen by nasal cannula, intravenous aminophylline, subcutaneous terbutaline every eight hours, and nebulized isoetharine every two hours. Spirometry was performed every six hours just prior to the patient's receiving the nebulized bronchodilator to ensure that baseline pulmonary functions were obtained. Lung function as measured by forced expiratory volume in one second (FEV_1) improved more rapidly and to a greater extent in the corticosteroid group compared with controls (118 ± 25 vs. 35 ± 22 percent over baseline at 24 hours).[6]

In addition, all of the patients who received corticosteroids achieved at least a ten percent improvement in FEV_1 compared with only four in the placebo group. Five of the patients who received placebo exhibited a deterioration in FEV_1 at 24 hours despite bronchodilator therapy. There were no distinguishing features in the placebo group between the patients who improved and those who did not. Thus, while not all patients with acute, severe asthma require corticosteroids, there are no distinguishing clinical characteristics enabling the clinician to discern those who require corticosteroids from those who would respond without corticosteriod treatment. Also, two of the patients in the corticosteroid group demonstrated a minimal response (<50 percent improvement) by 24 hours.[6] These phenomena have significant implications when evaluating the literature.

The relatively large variability in response rate makes it difficult to place much merit in studies that do not strictly adhere to good scientific principles (i.e., blinding, randomization). Studies using a small number of patients are likely to have a large beta error whether comparing differing dosages, corticosteroid preparations, or treatment versus no treatment. Because the airway obstruction in asthma is reversible and generally will improve over time, the rate of recovery is a more important endpoint than absolute recovery. Prevention of relapse, need for mechanical ventilation, and death are also viable endpoints. Although there has been considerable speculation in the literature on the role of corticosteroids in preventing death from asthma,[7] Fiel appropriately stated that there have been no controlled trials showing that institution of corticosteroids decreases death from acute, severe asthma.[1] Nor has the mortality rate from asthma declined since institution of corticosteroid therapy. The implication that corticosteroid therapy decreases mortality is derived from epidemiologic investigations of asthma deaths, which consistently show that many of the patients did not receive steroids or they were administered in inadequate dosages.[7]

There are also only two double-blind, randomized, placebo-controlled trials of children hospitalized for acute, severe asthma.[8,9] Pierson et al. compared three different intravenous corticosteroids (hydrocortisone, betamethasone, and dexamethasone) administered in equivalent glucocorticoid doses to placebo in 45 children who failed standard emergency room therapy. Patients were evaluated clinically and with blood gases and pulmonary function testing on admission and at 3, 12, and 24 hours after beginning study drugs. If the patient had decreasing arterial oxygen tension (PaO_2) or FEV_1, or increasing arterial carbon dioxide tension ($PaCO_2$) at three hours, the study assignment code was broken and the patient was reassigned to a steroid group if they were receiving placebo. Pulmonary function tests and clinical scores did not differ between the two groups at 12 and 24 hours of therapy. However, 7 of 15 patients in the placebo group required reassignment to a steroid group at 3 hours and no steroid patients required the treatment code to be broken. Thus, only those responding adequately would have been left in the placebo group. The steroid-treated groups had a significantly greater improvement in PaO_2 at 24 hours than the placebo group. There were no differences among the three steroids.[8]

Younger et al. gave methylprednisolone 2 mg/kg iv initially followed by 1 mg/kg q6h or placebo to 49 nonsteroid-dependent children 6–16 years old. The patients receiving corticosteroids demonstrated a more rapid improvement in clinical symptoms and forced expiratory flow rate during 25–75 percent of forced vital capacity. Fewer patients in the corticosteroid group experienced asthma relapse within one month of hospital discharge. Only two patients required their treatment code to be broken and were transferred to the intensive care unit; both had been randomized to the placebo group.[9]

One other double-blind, placebo-controlled trial was performed in children with severe, chronic asthma who were residents at a live-in facility. Sixteen patients received either prednisone 2 mg/kg/d po q6h or placebo following a sudden exacerbation of asthma not responding to beta-agonists. PEFRs were measured three times daily in each patient and the use of beta-agonists was quantitated. The prednisone group demonstrated a significant improvement in PEFR within 12 hours that reached near 85 percent of the predicted normal by 24 hours. The placebo group showed only minimal improvement in PEFR and required extra beta-agonist therapy for a greater period of time. Only one patient in the placebo group showed good improvement following completion of the study. All of the rest eventually required a course of high-dose corticosteroids.[10]

Interestingly, neither of the two studies often cited[2] for demonstrating no benefit for corticosteroids in acute, severe asthma were blinded,[11,12] and in only one was treatment randomly allocated.[11] Kattan et al. studied only 19 nonsteroid-dependent children hospitalized for acute, severe asthma compared with 45 patients in each of the double-blind, placebo-controlled trials discussed above.[8,9] Both treatment groups exceeded 50 percent of predicted

PEFRs by 24 hours,[11] a response rate equivalent to that seen for corticosteroid treatment in placebo-controlled trials.[6,10] Luksza reported his experience with adult asthmatics admitted to an intensive care unit over a three-year period. Three groups of 30 patients each were treated with either hydrocortisone 100 mg iv q2h or q6h or no corticosteroids. Previous corticosteroid administration was not an exclusion criterion. All patients received oxygen, intravenous aminophylline, and nebulized albuterol via intermittent positive pressure breathing every four hours. For analysis, the author divided the patients into four groups according to chronic corticosteroid usage and acute corticosteroid dosage. Six of the patients (20 percent) not receiving corticosteroids required mechanical ventilation, whereas only 7 (12 percent) receiving corticosteroids required mechanical ventilation. The statistical significance of this was not analyzed by the authors. The three groups receiving corticosteroids had higher mean ages than the nonsteroid group (32.1, 45.1, and 44.3 years vs. 28.7 years).[12]

OUTPATIENT STUDIES

Outpatient studies of corticosteroid use in acute asthma exacerbations consist of the following three basic formats: (1) administering a single dose of corticosteroid upon presentation to the emergency room; (2) administering a course of corticosteroids upon discharge from the emergency room or clinic; and (3) beginning a course of corticosteroids at home or clinic at the beginning of an exacerbation not completely responding to beta-agonists. A number of double-blind, placebo-controlled trials in both children[13-15] and adults [16] have shown the latter two kinds of studies to hasten recovery, prevent relapses, and decrease hospitalization rates. In infants less than 18 months of age, the data are less conclusive.

Tal et al. demonstrated the combination of a corticosteroid and $beta_2$ agonist to be superior to placebo or either agent alone in treating hospitalized infants with acute wheezing.[17] On the other hand, Webb et al. found that five days of oral prednisone did not alter the course of wheezing attacks in a group of infants who had a previous history of multiple wheezing attacks. However, they did not control for beta-agonist administration.[18] Both of these studies undoubtedly included some patients with bronchiolitis, a condition that may not respond to corticosteroids.[19] In an open, nonblind trial, Brunette et al. demonstrated that administering prednisone 1 mg/kg/d at the start and throughout a viral upper respiratory tract infection significantly decreased the number of days of wheezing, asthma attacks, emergency room visits, and hospitalizations in a select group of preschool asthmatic children with a history of asthma exacerbated by viral infections. Sixteen infants (aged 36.4 months) were compared with 16 control infants (40.4 months) whose parents did not want to use corticosteroids. Both groups were observed for two years. The treatment group received the prophylactic prednisone in the second year. The rates of emergency room visits and hospitalizations were significantly different between periods in the treatment group as well as between groups.[20]

The utility of initiating corticosteroids upon presentation to the emergency room or clinic remains more controversial. Littenberg and Gluck gave a single injection of methylprednisolone 125 mg or NaCl 0.9% as placebo to 97 adults presenting to an emergency room with an acute exacerbation of asthma. The patients remained in the emergency room for 1–12 hours (mean 4 hours). They reported a significantly better subjective response and decreased hospital admission rate (18.8 vs. 46.9 percent) in the subjects receiving methylprednisolone, despite no significant difference in the pulmonary function tests at the time of final dispensation. Although the mean FEV_1 values for the methylprednisolone group were not significantly different from the placebo group, they were greater and approached significant ($p = 0.068$). Unfortunately, the authors did not control beta-agonist administration in terms of dose or intensity.[21]

This is in conflict with the previous single-dose, double-blind, placebo-controlled trial reported by McFadden et al. They followed objective pulmonary function tests and clinical variables for six hours in 38 patients following an intravenous injection of hydrocortisone 250 mg, 500 mg, or 1 g, or placebo and detected no response to the corticosteroid above that produced by an aerosol beta-agonist. There also was no difference in whether the patient was discharged or admitted to the hospital.[22] Their results are consistent with other studies that also were unable to detect any improvement in pulmonary physiology in the first six hours following corticosteroid administration for acute severe asthma (see Figure 1 and discussion below).[6,8,23,24]

The disparity among the studies is most likely explained by the variability in time spent in the emergency room (up to 12 hours), the lack of specific, well-defined admission or discharge criteria, and the uncontrolled nature of the other therapies in the study by Littenberg and Gluck.[21] Also, the well-known euphoric effect of the corticosteroids could have provided the patients with a sense of well-being without an attendant objective physiologic improvement. This was first noted by Collins et al., whose patients reported significant subjective improvement 3.4 ± 1.67 hours following institution of hydrocortisone therapy, despite no measurable change in pulmonary functions until eight hours (Figure 1).[23] Schneider et al. reported admission rates

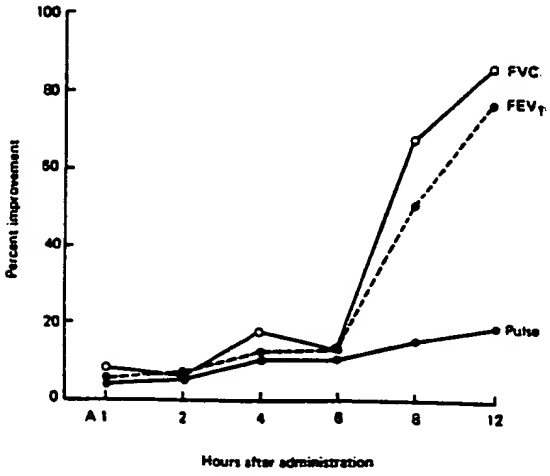

Figure 1. Rate of improvement after starting corticosteroid treatment in severe acute asthma.[23] FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity.

similar to those of Littenberg and Gluck in their study of 54 patients presenting to the emergency room for acute bronchospasm. They administered either methylprednisolone 30 mg/kg or NaCl 0.9% iv upon presentation in a double-blind fashion; however, each patient then received the same bronchodilator and spirometric monitoring protocol. The difference in hospital admission rate approached significance (19 percent for methylprednisolone vs. 44 percent for placebo, $p=0.078$). Unfortunately, although they monitored objective pulmonary functions, they did not report these results. They also did not exclude patients with chronic obstructive pulmonary disease.[25] More recently Stein and Cole reported the results of their randomized, double-blind, placebo-controlled study in 81 patients. All of their patients presented with acute, severe asthma and received either methylprednisolone 125 mg or NaCl 0.9% iv and had all other aspects of therapy and monitoring controlled. No difference was found in admission rates (13 percent placebo vs. 18 percent methylprednisolone), peak flow rate at disposition, rate of improvement in peak flow rate, or symptom scores.[26] The lower admission rates were most likely due to controlling all therapies and monitoring.[25]

Response Characteristics

Understanding the onset, rate, and duration of response to corticosteroids in acute, severe asthma is essential to establishing criteria for their appropriate use.

ONSET

Corticosteroids do not have a direct relaxing effect on bronchial smooth muscle.[4] Their influence on airway obstruction resides in their antiinflammatory effects and their ability to improve the smooth muscle responsiveness to beta$_2$-adrenergic agonists and endogenous catecholamines. Asthmatic patients may have desensitization and/or down-regulation (decreased number) of adrenergic receptors with decreased cyclic adenosine monophosphate (cAMP) response to beta$_2$-agonist stimulation and corticosteroids can prevent and reverse this phenomenon.[27] In addition, corticosteroids block extraneuronal uptake mechanisms for removal of catecholamines from receptors, thus further potentiating their effects.[4]

The antiinflammatory effects of corticosteroids require new protein synthesis with a lag time of one to four or more hours; however, not all of the effects are dependent on protein synthesis.[3] For example, elevation of cAMP occurs within minutes of the exposure of human lymphocytes to pharmacologic concentrations of corticosteroids in vitro.[28] They facilitate the formulation of a high-affinity receptor, leading to increased coupling with and activation of adenylate cylase,[29] as well as interfering with the extraneuronal uptake and inactivation of catecholamines.[30,31] In addition, glucocorticoids may enhance the effectiveness of cAMP by affecting cAMP protein kinase.[4]

Another important non-nuclear mechanism of action is through alterations in calcium flux. Corticosteroids appear to produce major changes in cellular metabolism by regulating calcium influx into cells. For example, rapid inhibition of adrenocorticotropic hormone (ACTH) secretion from pituitary cells results from steroid-induced inhibition of calcium entry.[4]

The time course of the corticosteroid response on airway obstruction therefore depends on the population studied, for example, chronic stable asthmatics versus patients experiencing status asthmaticus, and the relative importance of each mechanism in that clinical situation. In chronic stable asthmatics a single intravenous dose of a corticosteroid will improve the responsiveness to aerosol isoproterenol in one hour.[31] Pulmonary function tests in stable asthmatics begin to show improvement in one to three hours following administration of single doses of intravenous, oral, or inhaled corticosteroids with a maximum effect at six to nine hours.[4]

Collins et al. evaluated the onset and rate of recovery in patients hospitalized with acute, severe asthma and failing to have any improvement with bronchodilator therapy. The patients were treated only with intramuscular ACTH or intravenous hydrocortisone, oxygen, and intravenous fluids so that bronchodilators would not influence the response. Figure 1 illustrates the six-hour lag time prior to a measurable effect on pulmonary function.[23] This time lag has been confirmed in subsequent studies[6,8,24] and indicates a dominant role for the antiinflammatory effects of corticosteroids in acute, severe asthma. It may also explain why some patients who present with rapid onset of attacks without a significant inflammatory component may achieve adequate responses without corticosteroids.[6,11]

Although the delay in onset argues for early institution of corticosteroids in acute, severe asthma, it is also apparent that patient outcome will unlikely be altered by the immediate addition of corticosteroids in the emergency room or physician's office, and that they should be added only after an initial trial of intensive aerosolized bronchodilator therapy (at least three doses over one hour) has failed to completely resolve the attack. Although one also could argue that because a single dose of a corticosteroid is essentially nontoxic and patients who require corticosteroids cannot be clinically differentiated from those who do not, every patient should just be given a dose of corticosteroid immediately. Of course, the indication for any drug is not that it causes little harm, but that it is actually needed.

RATE OF RESPONSE

The optimal rate of response has not been defined. The high variability reported for response rate contributes to the difficulty in comparing and evaluating studies. Much of the variability is due to the heterogeneity of the patients and severity of illness, although some variability may be a result of corticosteroid dosage differences or other therapies. Some authors report percentage improvement from baseline; others report attainment of a percent of predicted normal or of the patient's best maximum. Small absolute improvements are magnified with the former method when the baseline measurements are small, as in acute asthma, whereas patients with higher baselines may appear to take longer to achieve the same percentage improvement.

DOSE-RESPONSE RELATIONSHIP

A number of dose-ranging studies have been published. For purposes of comparison, we have converted all dosages into methylprednisolone equivalents. The report by Haskell et al. is the most relevant to dosing hospitalized

patients. They compared intravenous methylprednisolone 60 mg (low), 160 mg (medium), and 500 mg (high) given as divided doses every six hours in a randomized, double-blind trial for 72 hours.[32] Their medium dose was similar to that administered by Fanta et al. (approximately 200 mg of methylprednisolone)[6] and their low dose was lower than that used by the Medical Research Council[5] (approximately 70 mg on day 1). Haskell et al. found both the medium- and high-dose groups to respond similarly with a significantly greater response than the low-dose group. The rate of response in the medium- and high-dose groups was similar to that reported by Fanta et al.,[6] with 80 percent of the patients in each group achieving 50 percent of predicted normal FEV_1 by 24 hours.[32]

The lack of any significant benefit from the high-dose regimen confirmed findings in two earlier trials.[33,34] However, each of these studies contained significant methodologic problems, including lack of randomization and blinding,[33] or too few patients (five in each group)[34] for adequate statistical power to determine negative results. This latter criticism also applies to Haskell et al.'s study, where their own power analysis determined they needed 84 patients to determine a 25 percent difference between groups.[32] Two more recent trials also failed to detect an advantage for high doses (exceeding methylprednisolone 160 mg/d).[35,36] In the only pediatric trial, Harfi et al. also failed to show an advantage of a high dose (300 mg/m^2 q6h) over a more moderate dose (30 mg/m^2 q6h).[37]

The minimum effective dose is unknown. The equivalent of methylprednisolone 60 mg/d appears insufficient.[32] The low-dose group in the study by Britton et al. received prednisone 80 mg/d for five days, but received a loading dose on day 1 equivalent to an additional 70 mg. As in most of the studies, the most rapid improvement occurred on the first day with a more gradual improvement over the next eight days.[33] Tanaka et al. gave only 80 mg/d to their low-dose group and found no difference from 500 mg/d. Both groups achieved 50 percent of their best FEV_1 on day 1, but the small number of subjects in each group (only five) precludes any conclusions.[34] In a study primarily designed to evaluate the need for intravenous administration, Harrison et al. concluded that prednisone 45 mg/d po was sufficient. However, they evaluated their patients for only 24 hours, and because all patients received a 45-mg loading dose as well as 15 mg q8h, all of the patients received at least 90 mg over the time in which they were evaluated.[38]

Sue et al. administered the equivalent of methylprednisolone 80 mg/d to 14 patients and none achieved 50 percent predicted within 24 hours.[24] However, most of their patients were receiving chronic oral corticosteroids, which was used as an exclusion criterion for other studies.[6,9,32] In a randomized, open trial of chronic steroid-dependent asthmatics, Krouse et al. demonstrated a similar slow recovery rate.[39] In contrast, three studies that did not exclude patients receiving chronic oral corticosteroids[10,36,38] showed rates of recovery similar to those reported by Fanta et al.[6] and Haskell et al. at similar dosages.[32]

The pediatric inpatient studies all administered the equivalent of methylprednisolone 3–4 mg/kg/d q6h for the duration of the evaluation period.[8,9,11,37] This dose is approximately two times the usual effective dose in the adult studies. There is no apparent explanation for this discrepancy, and the study by Loren et al., in children institutionalized with severe chronic asthma, demonstrated an excellent response with prednisone 2 mg/kg/d po, although it was essentially an outpatient study.[10]

DOSING FREQUENCY

The duration of action or response is the most important determinant of dosing frequency of any drug. This particular aspect of corticosteroid therapy in acute asthma has been inadequately studied and there are very few data in the available literature from which to draw conclusions. Unlike many other drugs, the duration of biological activity of the corticosteroids is not directly related to their plasma pharmacokinetics. Most of the corticosteroids used systemically in the management of acute, severe asthma have relatively short plasma half-lives (two to four hours).[4] Initial dosage recommendations for intravenous hydrocortisone (4 mg/kg q3–4h) were based on pharmacokinetic studies and the assumption that plasma concentrations of 11-hydroxycorticosteroid needed to exceed 100 μg/dL for a therapeutic effect.[40,41] This assumption was never proven and further pharmacodynamic studies have not been done.

Systemic corticosteroids are most often classified by their physiologic duration of action: (1) short-acting cortisone and hydrocortisone, 8–12 hours; (2) intermediate-acting prednisone and methylprednisolone, 12–30 hours; and (3) long-acting dexamethasone and betamethasone, 36–54 hours.[42] These durations are primarily determined by the ability of the drugs to produce hypothalamic-pituitary-adrenal (HPA) axis suppression and may not have any correlation to the antiasthmatic effects. The only studies designed to evaluate the time course of response to single doses of corticosteroids in asthma were performed in chronic asthmatics. These have been reviewed.[4] The peak effect on airway obstruction occurs 6–8 hours following either intravenous or oral doses of prednisolone or hydrocortisone and then slowly dissipates toward baseline over 12–24 hours. Storr et al. gave a single dose of either oral prednisolone or placebo to 140 children presenting to the hospital with acute, severe asthma. They were able to obtain adequate PEFR measurements in 29 matched pairs of children to evaluate the onset and duration of effect of the single dose of prednisolone. The PEFR peaked at 4–6 hours and began to decline by 7 hours, and was not different from placebo by 12 hours.[43]

Thus, currently available data, albeit very limited, suggest that multiple daily dosing may produce more optimal results than single daily dosing. All the clinical studies in children have administered the corticosteroid at least every 6 hours for the first 72 hours. Except for the more recent study by Ratto et al., who gave their lowest dosage regimen twice daily,[36] the clinical trials in adult asthmatics also used every-six-hour administration regimens.

CHOICE OF DRUG

Studies utilizing different corticosteroid preparations (i.e., hydrocortisone, prednisone, methylprednisolone) have failed to discern any significant differences in efficacy.[8,24,33,38] The one study specifically designed to compare intravenous hydrocortisone, methylprednisolone, and dexamethasone was nonblind and contained too few subjects (14) for sufficient statistical power to detect a difference.[24] Despite the lack of adequate clinical trials, differences do

exist among the preparations that may be relevant to their use in acute, severe asthma. Braude and Rebuck first reported that cortisol concentrations in bronchoalveolar lavage (BALF) fluid were similar to plasma concentrations following intravenous hydrocortisone.[44] They then found that methylprednisolone provided BALF concentrations superior to those of prednisone in patients with asthma and other inflammatory lung diseases.[45] This latter finding has since been confirmed in an animal model.[46]

Chernow et al. investigated corticosteroid-induced metabolic alkalemia and compensatory alveolar hypoventilation in healthy male baboons. They found that both intramuscular hydrocortisone and methylprednisolone significantly increased arterial pH and serum bicarbonate; dexamethasone did not. Only those animals receiving hydrocortisone showed a significant compensatory hypoventilation.[47] Baumgartner et al. reviewed the literature on corticosteroid-induced anaphylaxis and found that the majority of cases were associated with parenteral hydrocortisone.[48] Hydrocortisone-induced bronchoconstriction appears to be a particular problem in a subgroup of aspirin-sensitive asthmatics. These patients generally can be safely treated with methylprednisolone.[49]

MODE OF ADMINISTRATION

The initial report of the Medical Research Council utilized oral cortisol[5] and most of the outpatient studies also used oral corticosteroids.[10,13-16] Studies in chronic, stable asthmatics have shown only a marginally decreased time of onset and time to peak response for parenteral administration. In a randomized, double-blind, placebo-controlled trial, no advantage was seen for adding intravenous hydrocortisone to oral prednisolone therapy in hospitalized patients, even when stratified to rate of response.[38] Ratto et al. failed to demonstrate an advantage for intravenous administration over oral administration of methylprednisolone in a randomized trial of 77 adults hospitalized for status asthmaticus.[36]

DURATION OF THERAPY

How long a patient experiencing an acute exacerbation of asthma needs to be treated with systemic corticosteroids is a frequently asked question that has been inadequately studied. The answer appears to be: long enough to make the patient better and prevent a relapse and short enough to prevent significant toxicity. Although data exist to define the latter, the former remains undefined. Both inpatient and outpatient studies have utilized regimens encompassing a range of three days to as long as two weeks.[9,10,14,16,33,50] This has resulted in a myriad of dosing recommendations. The utilization of tapering dosing schemes in a number of studies further increases the confusion.[5,13,16,33,39]

The theoretical advantage of tapering the dosage is that it prevents rapid disease recrudescence or relapse. However, this theory is largely untested in acute asthma and current data lend little support. Lederle et al. compared the relapse rate in 43 adult male asthmatics over a 12-week period, divided into groups receiving either a 7-day or 7-week taper following an 8-day course of corticosteroids. The long taper group had a similar relapse rate, but a significantly higher incidence of adverse effects.[51] Young et al. administered only three days of corticosteroids to hospitalized asthmatic children and only 2 of 15 patients relapsed in the following four-week period.[9] Shapiro et al. reported similar results, with mild symptoms in 2 and wheezing in 1 of 13 children six days following completion of an eight-day tapering course in outpatients.[13]

TOXICITY

The adverse effects from excessive chronic glucocorticoid use are well known by clinicians. These include HPA axis suppression, growth retardation in children, Cushing's syndrome (buffalo hump, moon facies, striae, acne, hirsutism, peripheral wasting, and central obesity), fluid retention, hypertension, hypokalemia, osteoporosis, avascular necrosis of bone, hyperglycemia, myopathy, behavioral disturbances, increased risk of infections, and posterior subcapsular cataracts.[3,52] The development of these problems is dependent on both dose and duration.

It is generally assumed that short bursts of high-dose corticosteroids are not harmful.[1,3,52] Evaluation of dose-ranging studies for acute, severe asthma would seem to confirm this opinion.[32-36] Although generally devoid of acute adverse effects, high doses of hydrocortisone may aggravate preexisting heart failure or hypertension from sodium and water retention. Short bursts of prednisone have been associated with facial flushing. Excessive doses (methylprednisolone 1–2 g) may produce cardiac arrhythmias and sudden death through electrolyte shifts.[53] Very high doses of methylprednisolone (4 mg/kg q6h) has resulted in tetraplegia in a ten-year-old girl being treated for acute asthma.[54] Generalized myopathy has been associated with hydrocortisone doses exceeding 2.0 g/d,[52] and single doses of 8 mg/kg.[40] Central nervous system effects are more frequent at doses of prednisone >2 mg/kg/d.[52] In general, therapy for more than five days at doses exceeding usual physiologic cortisone production will cause some aberration in endogenous cortisol production.[3] A study in asthmatic children showed a blunted responsiveness of the HPA axis at three days, but not at ten days after completion of prednisone 2 mg/kg/d for five days.[55] In another study of children who were receiving prednisone 40–100 mg/m^2/d for 5–30 days as part of cancer chemotherapy, the HPA axis suppression took from one to more than seven days to completely recover.[56] There was no correlation with dose or duration of therapy and the time required for recovery. Shapiro et al. found no difference in the cosyntropin responsiveness between placebo and a 14-day tapering dose from methylprednisolone 32 mg in outpatient asthmatics treated for an acute exacerbation of asthma.[13]

The number of short "bursts" of systemic steroids that constitute chronic steroid use is not precisely known. At least eight short courses (ten days or less) of steroids per year produced similar decreases in trabecular bone density and increased risk of fractures as chronic daily or alternate-day steroid therapy over one year.[57] Dolan et al. investigated the effect of multiple bursts (less than seven days) of high-dose prednisone (1–2 mg/kg/d) for acute exacerbations on the HPA axis in 23 children with chronic asthma. Each child was studied at least 16 days after the last burst. Only those patients who received four or more bursts in the previous year demonstrated a subnormal response of the HPA axis to hypoglycemic stress or ACTH.[58]

Summary

Corticosteroids are potent antiinflammatory agents effective in the treatment of acute exacerbations of asthma. They have proven effective in preventing hospitalizations, enhancing the rate of recovery in outpatients as well as hospitalized patients, and decreasing relapse rates. Short courses of oral steroids for as little as three days have been effective for acute exacerbations not requiring hospitalization.[10,14] Four or fewer short bursts of oral steroids per year appear safe, but more data are required. Consideration should be given to starting patients on corticosteroids early in the course of upper respiratory tract infections if they have a history of severe asthma exacerbations during viral illnesses. Despite the findings from one study, the routine administration of corticosteroids to everyone entering an emergency room or clinic with an acute exacerbation of asthma is not warranted. Not all patients will require corticosteroids and one to two hours of intensive bronchodilator therapy will be all many patients require. Corticosteroid therapy is recommended for all patients not completely responsive to bronchodilator therapy whether or not they are to be admitted. All patients hospitalized for acute, severe asthma should receive corticosteroids.

A number of aspects concerning dosing remain unanswered. In nonhospitalized patients, the equivalent of methylprednisolone 1 mg/kg/d in two divided doses for children or 60 mg in two divided doses for adults has been used successfully. In general, the dose should be continued until the patient is asymptomatic. There is no available evidence to support or reject the use of a tapering course. However, by the end of a taper, patients are not on a therapeutic dose and may have an unnecessarily prolonged exposure. Short courses of ten days or less do not require consideration of tapering because of adrenal axis suppression.

Inpatient studies in both children and adults have generally used higher doses (3–4 mg/kg/d in four divided doses for children and 80–160 mg/d in two to four divided doses for adults) of methylprednisolone equivalent. The initial dose is usually continued for 48–72 hours until the patient significantly improves and then is changed to the outpatient dose for the remainder of the therapy (seven to ten days). Intravenous administration is unnecessary unless the patient is unable to take oral medication. We recommend methylprednisolone because of the extensive clinical experience with its use, and the lack of mineralcorticoid effects seen with hydrocortisone. Its intermediate duration should produce less adrenal suppression than the longer acting dexamethasone, and it may have an advantage in penetrating the lung. Higher dosages should be discouraged because of the increased risk of toxicities and no evidence of greater efficacy over these more moderate doses. ≏

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EXTRACTO

Los corticosteroides se han utilizado en el tratamiento agudo de asma severa desde el comienzo de la década de los 50. En numerosos estudios al azar, doble ciegos y controlados con placebo se ha comprobado la eficacia de estos medicamentos en pacientes adultos y en niños. Sólo en estudios poco rigurosos se ha encontrado que estos fármacos no son beneficiosos. Aunque se ha evaluado relativamente bien la dosis, vía de administración y el inicio de la respuesta a los corticosteroides, se necesitan más estudios para determinar la duración del tratamiento, la necesidad de reducir lentamente la dosis del medicamento y el riesgo asociado a dosis múltiples altas por períodos cortos de tiempo. El administrar corticosteroides al inicio de los ataques agudos de asma ha disminuido la necesidad de hospitalizar a cierto grupo de pacientes. Sin embargo, no se recomienda administrar estos medicamentos a todo paciente que se presente a una sala de emergencia. Inicialmente se debe comenzar con un tratamiento agresivo de broncodilatadores. Se administran corticosteroides cuando el paciente no presenta, en uno a dos horas, una respuesta adecuada a los broncodilatadores. Tratamientos con corticosteroides por tres a cinco días han sido efectivos en pacientes ambulatorios y por siete a diez días en pacientes hospitalizados (encamados). La duración del tratamiento depende del individuo y su respuesta al uso de los corticosteroides.

ANNETTE PÉREZ

RESUME

Les corticostéroides sont utilisés pour traiter l'asthme sévère aigu depuis les années cinquante. Plusieurs études randomisées à double insu, avec un placebo pour contrôle chez les adultes et les enfants ont démontré que les corticostéroides étaient efficaces. Seulement quelques résultats d'études moins bien structurées n'ont pas demontré d'effets bénéfiques. Alors que le temps de réponse, la dose et le mode d'administration ont été relativement bien définis, d'autres aspects (i.e., la durée de traitement, le besoin de diminuer les doses progressivement) nécessitent d'autres études. L'introduction rapide des corticostéroides dans une population bien définie de patients diminuera le besoin d'hospitalisation. Cependant, l'administration de corticostéroides à chaque patient se présentant au cabinet du médecin ou à la salle d'urgence avant d'avoir tenté les bronchodilatateurs de façon agressive est injustifiée. Tous les patients ne répondant pas complètement ou étant incapable de maintenir une réponse complète dans les une à deux heures suivant la thérapie agressive avec les bronchodilatateurs devraient recevoir un traitement avec les corticostéroides. Des traitements aussi courts que de trois à cinq jours ont prouvé leur efficacité chez les patients non hospitalisés alors que les patients hospitalisés sont traités pour sept à dix jours. La durée de la thérapie dépend de la réponse individuelle de chaque patient.

CHANTAL GUEVREMONT

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